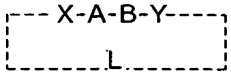
Claims

1. A compound having the general formula I

(I) 

where the dashed line indicates that formula I is optionally cyclic, and the bonds shown represent covalent bonds;

and wherein A represents a chemical moiety having an amino group (radical) and a carboxy group that forms part of the peptide bond connecting A to X and B;

B represents a chemical moiety having an amino group (radical) and a carboxy group that forms part of the peptide bond connecting B to A and Y;

X represents a peptide sequence of from 1 to 3 amino acid residues which independently may be an L or D form when Y represents a C-terminal peptide sequence of from 2 to 5 amino acid residues which may independently be L- or D-forms;

or X represents an N-terminal modification of the group A-B when Y represents a C-terminal peptide sequence of from 2 to 5 amino acid residues which may independently be L- or D-forms; or

X represents a peptide sequence of from 2 to 5 amino acid residues which may independently be L- or D-forms when Y represents a C-terminal peptide sequence of from 1 to 3 amino acid residues which independently may be an L or D form;

and when formula I represents a linear peptide X is optionally chemically modified at its N-terminal,
and L is an optional linking group comprising from 0 to 8 backbone atoms;

and a mirror image or a retro analogue of formula I, or a derivative of formula I which is a pharmaceutically acceptable salt, an alkyl, aryl or aralkyl ester, an amide, a mono or disubstituted amide where the substituent is an alkyl, an aryl or an aralkyl, a hydrazide, or an alcohol;
with the proviso that the compounds
with the proviso that the compounds
H-Gly-Pro-Leu-Gly-Pro-OH,
H-Pro-4Hyp-Gly-Ala-Gly-OH,

N-3-(4-hydroxyphenyl)propionyl-Pro-4Hyp-Gly-Ala-Gly-OH,
N-3-phenylpropionyl-Pro-4Hyp-Gly-Ala-Gly-OH,
N-3-phenylpropyl-Pro-4Hyp-Gly-Ala-Gly-OH,
N-3-(4-hydroxyphenyl)propionyl-Pro-4Hyp-Gly-Ala-OH,
N-3-(4-hydroxyphenyl)propionyl-Pro-4Hyp-Gly-OH,
N-3-(4-hydroxyphenyl)propionyl-Pro-4Hyp-OH,
N-3-(4-hydroxyphenyl)propionyl-Pro-Pro-Gly-Ala-Gly-OH,
H-Gly-Ala-Gly-4Hyp-Pro-Tyr-NH_2,
H-Gly-Ala-Gly-4Hyp-Pro-Tyr-OH,
H-Ala-Gly-4Hyp-Pro-Tyr-NH_2,
H-Gly-Sar-Pro-Gly-Ala-Gly-OH,
H-Gly-Pro-Sar-Gly-Ala-GlyOH,
H-Gly-Sar-Sar-Gly-Ala-Gly-OH,
H-Gly-Ala-Gly-Hyp-Pro-Tyr(3-I)-NH_2,
H-Gly-Ala-Gly-Hyp-Pro-Tyr(3-F)-NH_2
H-Gly-Ala-Gly-Hyp-Pro-Tyr(3-Cl)-NH_2
H-Gly-Ala-Gly-Hyp-Pro-Tyr(3-Br)-NH_2
H-Arg-Ala-Gly-Hyp-Pro-Tyr-NH_2
H-Val-Ala-Gly-Hyp-Pro-Tyr-NH_2
H-Ala-Ala-Gly-Hyp-Pro-Tyr-NH_2
H-Gly-Ala-Gly-Hyp-His-Tyr-NH_2
H-Gly-Ala-Gly-Hyp-Pro-Phe-NH_2
Cyclo(CF_3C(OH)-Gly-Ala-Gly-4Hyp-Pro-Tyr-CONH), and
Cyclo(CO-Gly-Ala-Gly-4Hyp-Pro-Tyr-CONH).
are not covered by the general formula I.

2. A compound according to claim 1 wherein said covalent bonds are selected from peptide bonds, disulphide bonds, ester bonds, reduced amide bonds, alkoxy bonds, oxycarbonyl bonds, and acyloxyalkoxy bonds.

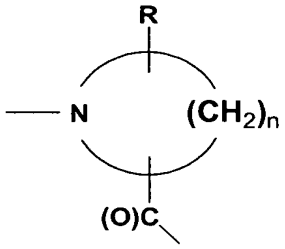
3. A compound according to the preceding claim wherein said covalent bond is a peptide bond.

4. A compound according to any one of the preceding claims wherein A and B each represents an amino acid or an amino acid derivative having functional amino and carboxy groups.

5. A compound according to any one of claims 1 to 4 wherein A-B represents a dipeptide

selected from the group consisting of Sar-Sar, Sar-Hyp, Hyp-Sar, Pro-Sar, Sar-Pro, Pro-Hyp, Pro-Pro, Hyp-Pro, and Hyp-Hyp, where Pro and Hyp independently may be an L or D form, where the ring structure of Pro and Hyp is optionally substituted with halogen, nitro, methyl, amino, or phenyl, and Hyp represents 3-hydroxyproline or 4-hydroxyproline, or one or both of the amino acid residues of A-B is a Sar, or N-cyclohexylglycine residue.

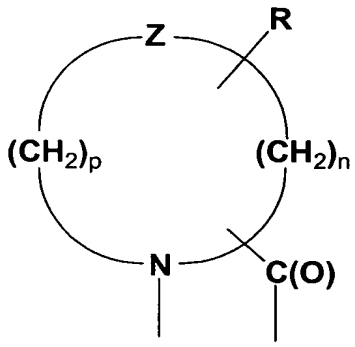
6. A compound according to any one of claims 1 to 3 wherein the groups A and B each independently represents a group of the formula II



(II)

wherein n is an integer having the value 3, 4, or 5, and R represents an optional substituent, preferably selected from the group consisting of halogen, phenyl, hydroxy, NH_2, and C(1-6)alkyl optionally substituted with halogen.

7. A compound according to any one of claims 1 to 3 wherein the groups A and B are represented by the formula IIa



IIa

Wherein n is an integer having the value 0, 1, 2, and 3, p is an integer having the value 0, 1, 2, and 3, Z represents O or S, and R represents an optional substituent, preferably selected from the group consisting of halogen, phenyl, hydroxy, NH_2, and C(1-6)alkyl.

8. A compound according any one of the two preceding claims wherein R is selected from the group consisting of F, Cl, Br, phenyl, OH, NH_2, CH_3, and CF_3.

9. A compound according to any one of the preceding claims wherein A and B independently represents an amino acid residue having a saturated carbocyclic structure of 4, 5 or 6 members and where in said carbocyclic structure further comprises one or more heteroatoms.

10. A compound according to the preceding claim wherein said heteroatoms is selected from the group consisting of N, O and S.

11. A compound according to the preceding claim selected from the group consisting of L and D forms and derivatives of Prolin having one or more substituents in the 3, 4 or 5 position, said substituents being selected from hydroxy, amino and phenyl.

12. A compound according to any one of claims 6 and 7 wherein A and B is selected from the group consisting of N- and C(O)- radicals of the following compounds:
D/L-azetidin-3-carboxylic acid,
D/L-azetidin-2-carboxylic acid,
D/L-Indolin-2-carboxylic acid,
D/L-1,3-dihydro-isoindol-1-carboxylic acid,
D/L-thiazolidin-4-carboxylic acid,
D/L-pipecolinic acid,
D/L-Nipecotinic acid,
Isonipecotinic acid,
L/D-2-carboxymorpholin,
L/D-1,2,3,4-tetrahydroquinolin-3-carboxylic acid,
L/D-1,2,3,4-tetrahydroquinolin-3-carboxylic acid, and
4-carboxy-4-phenyl-piperidin.

13. A compound according to any one of the preceding claims wherein formula I represents a linear peptide wherein said chemical modification of the N-terminal of X is an acylation with an optionally substituted straight, branched, saturated, unsaturated, or aromatic C(1-22)carboxylic acid where the substitutent is selected from hydroxy, halogen, C(1-6)alkyl, nitro or cyano and may be situated on the carbon chain or the aromatic moiety.

14. A compound according to the preceding claim wherein said C(1-22)carboxylic acid is a C(1-7)carboxylic acid selected from the group consisting of acetic acid; propionic acid, butyric acid and isomers thereof; and benzoic acid.

15. A compound according to any one of the preceding claims wherein formula I represents a linear peptide wherein said chemical modification of the N-terminal of X is an alkylation with an optionally substituted C(1-22)alkyl or aryl C(1-22)alkyl where the substitutent is selected from hydroxy, halogen, C(1-6)alkyl, nitro or cyano and may be situated on the carbon chain or the aromatic moiety.

16. A compound according to the preceding claim wherein said C(1-22)alkyl is a C(1-6)alkyl and said aryl C(1-22)alkyl is an aryl C(1-3)alkyl, respectively.

17. A compound according to the preceding claim wherein said C(1-6)alkyl or a C(7-9)aralkyl is selected from the group consisting of methyl, ethyl, propyl, butyl, phenylpropyl, 2-hydroxyphenylpropyl, and 4-hydroxyphenylpropyl.

18. A compound according to claim 15 wherein X represents one amino acid residue.

19. A compound according to the preceding claim wherein said amino acid residue is selected from the group consisting of L-Tyr and D-Tyr optionally acylated with a C(1-4)carboxylic acid when Y represents a C-terminal peptide sequence of from 2 to 5 amino acid residues as defined in claim 1.

20. A compound according to the preceding claim wherein said C(1-4)carboxylic acid is acetic acid.

21. A compound according to any one of claims 12 to 20 wherein A-B is selected from the group consisting of Pro-Hyp, Pro-Pro, Hyp-Pro, and Hyp-Hyp where Pro and Hyp independently may be an L or D form.

22. A compound according to the preceding claim wherein Hyp represents L-4Hyp.

23. A compound according to any one of claims 12 to 22 wherein Y represents a peptide of 3 or 4 amino acid residues being independently L- or D-forms.

24. A compound according to the preceding claim having Sar or Gly at its C-terminal.

25. A compound according to any one of claims 18 to 27 wherein Y represents a peptide sequence selected from the group consisting of
Gly-L-Ala-Gly,
Gly-L-Ala-Gly,
Gly-D-Ala-Gly,
Gly-D-Ala-Gly, and
Sar-Aib-Sar.

26. A compound according to any one of claims 1 to 11 wherein formula I represents a linear peptide and X represents an N-terminal modification of the group A-B.

27. A compound according to the preceding claim wherein said modification is an acylation of the N-terminal of A-B with a compound selected from the group consisting of phenylpropionic acid and derivatives thereof; phenylacetic acid and derivatives thereof; phenoxyacetic acid and derivatives thereof; benzoylglycine and derivatives thereof; and phenylglycine and derivatives thereof.

28. A compound of formula I selected from the group consisting of
Ac-L-Tyr-L-Pro-L-4Hyp-Gly-L-Ala-Gly,
Ac-D-Tyr-D-Pro-D-4Hyp-Gly-D-Ala-Gly,
4HPPA-L-Pro-L-4Hyp-Gly-L-Ala-Gly, and
a pharmaceutically acceptable salt, an alkyl ester, an amide, an alkylamide, an aryl amide, a dialkylamide, an aryl/alkyl amide, a hydrazide, or an alcohol thereof.

29. A compound according to any one of claims 1 to 11 wherein formula I represents a cyclic compound.

30. A compound according to the preceding claim wherein said cyclic compound is a cyclic peptide sequence comprising all L-forms, all D-forms, or a sequence of mixed L- and D-forms of the amino acid residues thereof.

31. a compound according to the preceding claim wherein A-B is selected from the group consisting of
Pro-Hyp, Pro-Pro, Hyp-Pro, and Hyp-Hyp where Pro and Hyp independently may be an L or D form and Hyp preferably represents 4-hydroxyproline.

32. a compound according to the preceding claim wherein A-B represents unsubstituted L-Pro-L-4Hyp, L-4Hyp-L-Pro, D-Pro-D-4Hyp, or D-4Hyp-D-Pro.

33. A compound according to any one of claims 31 to 34 wherein X represents a single amino acid residue.

34. A compound according to the preceding claim wherein X represents L-Tyr or D-Tyr optionally further substituted with halogen, phenyl, hydroxy, NH_2, C(1-6)alkoxy, aryloxy, and C(1-6)alkyl optionally substituted with halogen, at its aromatic ring when Y represents a peptide of 3 or 4 amino acid residues being independently L- or D-forms.

35. A compound according to the preceding claim wherein Y has Asp, Asn, Gln or Glu at its C-terminal.

37. A compound according to the preceding claim wherein Y represents a peptide sequence selected from the group consisting of
Gly-L-Ala-L-Asn,
Gly-D-Ala-L-Asn,
Gly-L-Ala-Gly-L-Asn,
Gly-L-Ala-Gly-D-Asn,
Gly-L-Ala-L-Gln,
Gly-L-Ala-Gly-L-Gln,
Gly-L-Ala-Gly-D-Gln,
Gly-D-Ala-D-Asn,
Gly-D-Ala-Gly-D-Asn,
Gly-D-Ala-Gly-L-Asn,
Gly-D-Ala-D-Gln,
Gly-D-Ala-Gly-D-Gln,
Gly-D-Ala-L-Gln,
Gly-D-Ala-Gly-D-Gln,
Gly-L-Ala-L-Asp,
Gly-D-Ala-L-Asp,
Gly-L-Ala-Gly-L-Asp,
Gly-L-Ala-Gly-D-Asp,
Gly-L-Ala-L-Glu,
Gly-L-Ala-Gly-L-Glu,

Gly-L-Ala-Gly-D-Glu,
Gly-D-Ala-D-Asp,
Gly-D-Ala-Gly-D-Asp,
Gly-D-Ala-Gly-L-Asp,
Gly-D-Ala-D-Glu,
Gly-D-Ala-Gly-D-Glu,
Gly-D-Ala-L-Glu,
Gly-D-Ala-Gly-D-Glu.

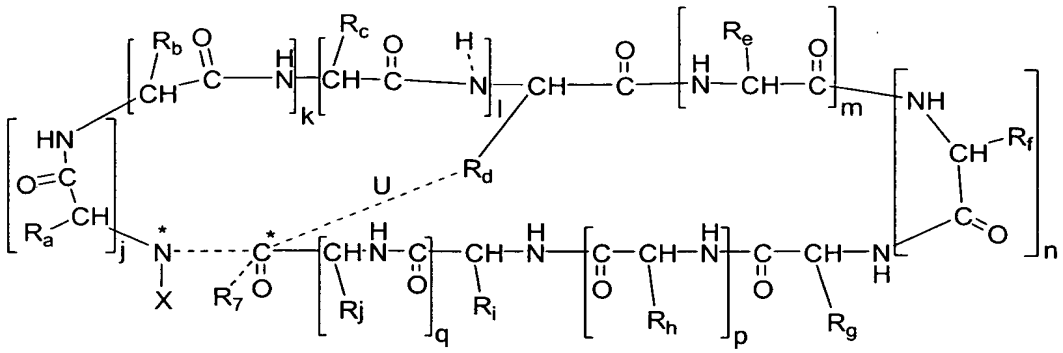
38. A compound according to wherein X represents a peptide sequence selected from the group consisting of
Gly-L-Ala-L-Asp,
Gly-L-Ala-Gly-L-Asp,
Gly-L-Ala-L-Glu,
Gly-L-Ala-Gly-L-Glu,
Gly-D-Ala-D-Asp,
Gly-D-Ala-Gly-D-Asp,
Gly-D-Ala-D-Glu,
Gly-D-Ala-Gly-D-Glu,
and Y represents a single amino acid residue.

39. A compound according to the preceding claim wherein Y represents L-Tyr or D-Tyr optionally further substituted with halogen, phenyl, hydroxy, NH_2, C(1-6)alkoxy, aryloxy, and C(1-6)alkyl optionally substituted with halogen, at its aromatic ring.

40. A compound of formula I where the groups X and Y are connected via a peptide bond or a disulphide bond to form a cyclic compound.

41. A compound of the general formula XII

(XII)



representing a peptide sequence wherein the amino acid residues may be D- and/or L-forms, and having the N-terminal at N* and the C-terminal at C* and being optionally cyclic via a covalent bond between N* and C* as shown by a broken line or between R_d and C* as shown by the broken line U; and wherein

X represents an N-terminal moiety such as a photoprobe capable of being bond to the amino terminal N*, or an acyl group derived from a C(2-22)alkyl carboxylic acid, such as acetic acid, propionic acid, butyric acid and other fatty acids, such as behenic acid, optionally substituted with one or more substituents selected from the group consisting of hydroxy, halogen, C(1-6)alkyl, nitro and cyano; or X represents hydrogen;

R_7 represents OH, NH_2, $NHNH_2$ or OR_8 when the bond between N* and C* is missing, or R_7 is absent when there is a bond between N* and C*;

R_8 represents H or a straight or branched C(1-6)alkyl group, an aryl or an aralkyl group.

R_a represents the amino acid side chain of Hyp or Pro;

R_b represents the amino acid side chain of Hyp or Pro;

R_c represents the amino acid side chain of Gly, Sar, an aromatic amino acid side chain optionally substituted with one or more hydroxy, halogen or lower alkoxy group in the aromatic ring;

R_d represents the amino acid side chain of Ala, Gly, Glu, Asp, Dab, Dapa, Lys, Asn, Gln, Orn, or Cys;

R_e represents the amino acid side chain of Ala;

R_f represents the amino acid side chain of Ala, Sar or Gly;

R_g represents any amino acid side chain except the side chain of L-4Hyp or a moiety of formula II or Iia;

R_h represents the amino acid side chain of Ala, or R_g represents a moiety of formula II or IIa;

R_i represents the amino acid side chain of Gly or R_i represents an aromatic amino acid optionally substituted with one or more halogen groups in the aromatic ring;

R_j represents Asn, Gln, Asp, Glu, Cys or Tyr;

and each of j, k, l, m, n, p and q is independently 0 or 1;
and the retro form, all D form, or retro all-D form of the peptide sequence of formula XII, and
salts and amides thereof.

42. A compound according to the preceding claim wherein X is selected from the group consisting of Ac and the photoprobes ASAL optionally iodinated in position 5 to yield the group 2-hydroxy-4-azido-5-iodo benzoyl, and AB.

43. A compound according to any one of the two preceding claims wherein R_7 is NH_2.

44. A compound according to any one of the three preceding claims wherein R_a is the amino acid side chain of Pro.

45. A compound according to any one of the four preceding claims wherein R_b is the amino acid side chain of Hyp.

46. A compound according to any one of the five preceding claims wherein R_c is the amino acid side chain of Gly or Tyr.

47. A compound according to any one of the six preceding claims wherein R_d is selected from the group consisting of the amino acid side chain of Gly, Asp or Glu, Dapa and Dab.

48. A compound according to any one of the seven preceding claims wherein R_f is Ala or Gly.

49. A compound according to any one of the eight preceding claims wherein R_g is the amino acid side chain of Pro, Asn or Gly.

50. A compound according to the preceding claim wherein R_g is the amino acid side chain of Asn, Gly, D-4Hyp or L-/D-Pro when formula XII represents a linear peptide, or when formula XII represents a peptide cyclised between N* and C* then R_g represents the amino acid side chain of L-/D-4Hyp or L-/D-Pro.

51. A compound according to any one of the ten preceding claims wherein R_h is the amino acid side chain of Ala when U is missing, or R_h is Pro or Hyp when U is present.

52. A compound according to any one of the eleven preceding claims wherein R_i is preferably Tyr, Phe, Trp, Nal optionally substituted with one or more hydroxy, F or Cl, in the aromatic ring.

53. A compound according to any one of the twelve preceding claims wherein R_j is selected from the group consisting of the amino acid side chain of Asp, Glu, and Tyr.

54. A linear peptide according to claim 41 of formula XII which is an retro all-D form.

55. A peptide compound of formula XII consisting of between 3 and 9 amino acid residues, more preferably between 3 and 7 amino acid residues and wherein j and k are preferably 0 when U is present, j and k are preferably 1 when U is missing and formula XII represents a cyclic peptide, m is preferably 0 when U is missing, p is preferably 1 when U is present, and q is preferably 0 when U is present.

56. A compound according to claim 1 or 43 and having the general formula XIII

(XIII) $X\text{-}(G')_a\text{-}A\text{-}G'\text{-}(Px)_2\text{-}(Y')_b\text{-}R_7$

specifying a peptide sequence wherein the amino acid residues may be L and/or D forms, and
wherein
X represents H or Ac;
G' represents a glycine residue or a glycine analogue such as Sar;
A represents alanine;
Px represents an amino acid residue of formula II or IIa such as Hyp or Pro;
Y' represents tyrosine or phenylalanine optionally substituted in the phenyl ring with halogen or hydroxy;
a and b are independently 0 or 1,
R_7 represents OH, NH_2, $NHNH_2$, Asn-NH_2, or Gln-NH_2;
and retro forms thereof and salts thereof.

57. A compound according to the preceding claim wherein X represents Ac and all amino acid residues are L-forms.

58. A compound according to any one of the two preceding claims wherein G' is glycine.

59. A compound according to any one of the three preceding claims wherein Px is Pro.

60. A compound according to any one of the four preceding claims wherein Y' is Tyr.

61. A compound according to any one of the five preceding claims wherein R_7 is NH_2.

62. A retro compound of formula XIII having the formula XIIIa: $X-(Y')_b-(Px)_2-G'-A-(G')_a-R_7$ wherein all amino acid residues are D-forms and wherein all symbols have the same meaning as defined above for formula XIII.

63. A peptide compound of formula XIII wherein at least one Px residue is a D-amino acid and the rest are L-amino acids.

64. A cyclic sequence of formula XIII wherein X represents H, R_7 represents Asn or Gln having a covalent bond to Y' which represents Tyr, b is 1, and a is 1.

65. A compound of formula 2: $H-GAG-(Pa)_2-NH_2$ as defined herein or a salt thereof.

66. A compound according to the preceding claim selected from the group consisting of
H-Gly-Ala-Gly-D-Hyp-Pro-Tyr-NH_2,
H-Gly-Ala-Gly-D-Pro-Pro-Tyr-NH_2,
H-Gly-Ala-Gly-D-Pro-Ala-Tyr-NH_2,
H-Gly-Ala-Gly-Gly-D-Pro-Tyr-NH_2,
H-Gly-Ala-Gly-D-Hyp-Ala-Tyr-NH_2,
H-Gly-Ala-Gly-D-Hyp-D-Pro-Tyr-NH_2, and pharmaceutically acceptable salts thereof.

67. A compound of formula 3: $H-GAG-(Px)_2-Y-NH_2$ as defined herein or a salt thereof.

68. A compound according to the preceding claim selected from the group consisting of
H-Gly-Ala-Gly-NCG-Pro-Tyr-NH_2,
H-Gly-Ala-Gly-T4C-Pro-Tyr-NH_2,
H-Gly-Ala-Gly-A2C-Pro-Tyr-NH_2,
H-Gly-Ala-Gly-PC-Pro-Tyr-NH_2, and pharmaceutically acceptable salts thereof.

69. A compound of formula 8: H-G'-A-G'-(Px)2-Y-NH_2 as defined herein or a salt thereof.

70. A compound according to the preceding claim selected from the group consisting of H-Sar-Ala-Sar-Hyp-Pro-Tyr-NH_2,
H-Gly-Ala-Sar-Hyp-Pro-Tyr-NH_2, and pharmaceutically acceptable salts thereof.

71. A compound of formula 6: X-G-D-A-G-(D-Px)$_2$-D-Y-NH$_2$ as defined herein and salts thereof.

72. A compound according to the preceding claim selected from the group consisting of
H-Gly-D-Ala-Gly-D-Hyp-D-Pro-D-Tyr-NH$_2$,
H-Gly-D-Ala-Gly-D-Hyp-D-Pro-D-Tyr-D-Asp-OH,
Ac-D-Tyr-D-Pro-D-Hyp-Gly-D-Ala-Gly-NH$_2$,
Ac-D-Tyr(3,5-di-I)-D-Pro-D-Hyp-Gly-D-Ala-Gly-NH$_2$,
Ac-D-Tyr(phenyl ring mono-iodo substituted)-D-Pro-D-Hyp-Gly-D-Ala-Gly-NH$_2$,
Ac-D-Tyr-D-Pro-D-Hyp-(12,13C,15N-Gly)-D-Ala-(1,213C,15N-Gly)-NH$_2$, and pharmaceutically acceptable salts thereof.

73. A compound of formula 9: X-(Y)p-(Px)$_2$-GAG-NH$_2$ as defined herein and salts thereof.

74. A compound according to the preceding claim selected from the group consisting of
ASAL-Pro-Hyp-Gly-Ala-Gly-NH$_2$,
ASAL(mono-iodo substituted)-Pro-Hyp-Gly-Ala-Gly-NH$_2$,
AB-Tyr-Pro-Hyp-Gly-Ala-Gly-NH$_2$,
AB-Tyr(3,5-di-I)-Pro-Hyp-Gly-Ala-Gly-NH$_2$, and pharmaceutically acceptable salts thereof.

75. A compopund of formula 10: Cyclo(-GAG-(Px)$_2$-Y-N/Q-) as defined herein and salts thereof.

76. A compound according to the preceding claim selected from the group consisting of
cyclo(-Gly-Ala-Gly-Hyp-Pro-Tyr-Gln-),
cyclo(-Gly-Ala-Gly-Hyp-Pro-Tyr-Asn-),
cyclo(-Gly-Ala-Gly-Pro-Pro-Tyr-Asn-), and pharmaceutically acceptable salts thereof.

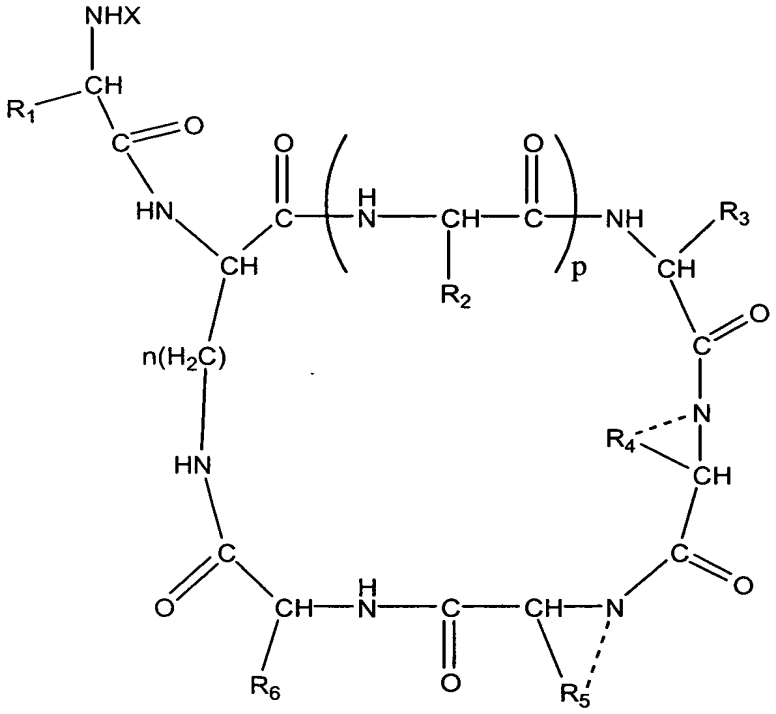
77. A compound of formula 11: Cyclo(-Y-(Px)$_2$-GA-(G)$_q$-N/Q-) as defined herein and salts thereof.

78. A compound according to the preceding claim selected from the group consisting of
Compound 3 cyclo(-Tyr-Pro-Hyp-Gly-Ala-Gly-Asn-),
Compound 4 cyclo(-Tyr-Pro-Hyp-Gly-Ala-Asn-),
cyclo(-Tyr(3-I, 5-I)-Pro-4Hyp-Gly-Ala-Gly-Asn), and pharmaceutically acceptable salts thereof.

79. A compound of formula 12: X-Zd-G(N/Q)Y-NH$_2$ as defined herein and salts thereof.

80. A compound according to the preceding claim selected from the group consisting of H-Gly-Ala-Gly-Asn-Tyr-NH_2,
Ac-Gly-Asn-Tyr-NH_2,
H-Gly-Asn-Tyr-NH_2,
Ac-Ala-Gly-Asn-Tyr-NH_2,
H-Ala-Gly-Asn-Tyr-NH_2, and pharmaceutically acceptable salts thereof.

81. A cyclic peptide compound of formula XII further characterised in having the general formulae XIV:



XIV

wherein

X represents H or an N-terminal moiety such as a photoprobe capable of binding to the N terminal or an acylation with a C(2-22)alkyl carboxylic acid, such as acetic acid, propionic acid, butyric acid and other fatty acids such as behenic acid, being optionally substituted with one or more substituents selected from the group consisting of hydroxy, halogen, C(1-6)alkyl, nitro and cyano;

R_1 represents H or CH_3;

R_2 and R_3 are different or the same and represent any possible amino acid side chain;

-------- represents an optional bond;

R_5 and R_4 represent any possible amino acid side chain or when the optional bond is present R_5 and R_4 represent together with the attached C and N atoms a proline ring which is optionally substituted with OH, preferably in the 4-position, or R_5 and R_4 represent together with the attached C and N atoms a moiety of formula II or IIa above;
R_6 represents an aromatic amino acid side chain optionally substituted in the aromatic ring with one or more substituents selected from halogen, nitro and hydroxy;
p is 0 or 1;
n is 1, 2, 3 or 4;
and salts thereof.

82. A compound according to the preceding claim wherein X represents H or the photoprobe groups AB or ASAL which is optionally iodinated as described herein.

83. A compound according to any one of the two preceding claims wherein R_1 represents H.

84. A compound according to any one of the three preceding claims wherein R_2 and R_3 are different or the same and represent H or CH_3.

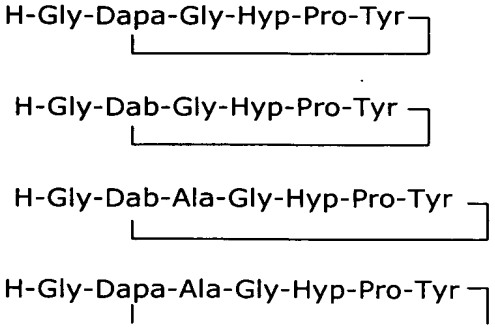
85. A compound according to any one of the four preceding claims wherein R_5 and R_4 represent together with the attached C and N atoms Pro or Hyp.

86. A compound according to any one of the five preceding claims wherein R_6 represents Tyr.

87. A compound according to any one of the six preceding claims wherein p is 1.

88. A compound according to any one of the seven preceding claims wherein n is 1.

89. A compound of formula XIV selected from the group consisting of



H-Gly-D-Dapa-Gly-D-Hyp-D-Pro-D-Tyr

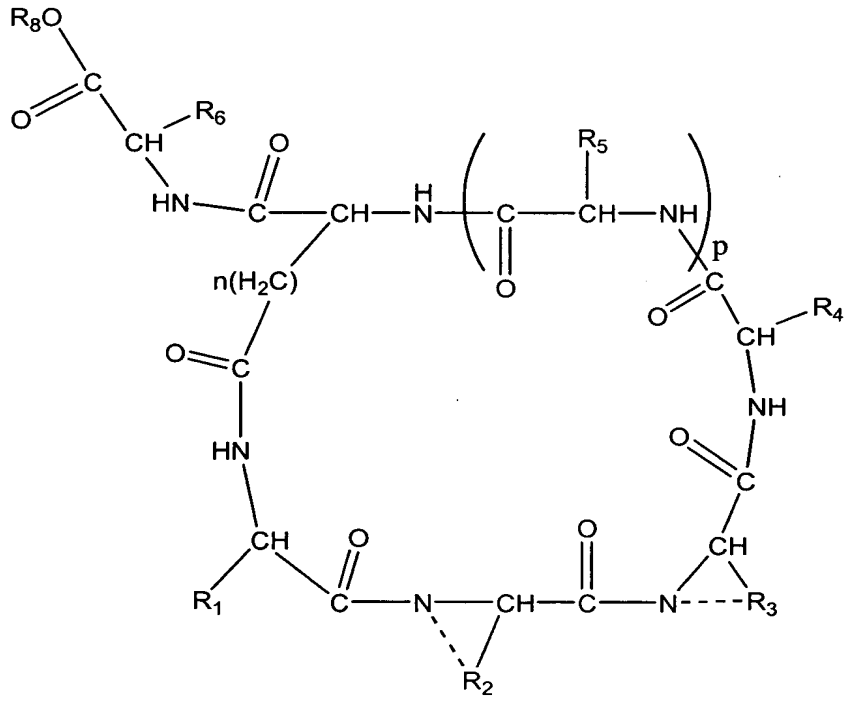
H-Gly-D-Dab-Gly-D-Hyp-D-Pro-D-Tyr

H-Gly-D-Dab-D-Ala-Gly-D-Hyp-D-Pro-D-Tyr

H-Gly-D-Dapa-D-Ala-Gly-D-Hyp-D-Pro-D-Tyr

and pharmaceutically acceptable salts thereof.

90. A compound of formula XII further characterised by the general formula XV



XV

Wherein R_8 represents H or a C(1-6)alkyl group;

R_6 represents H or CH_3;

R_4 and R_5 are different or the same and represent any possible amino acid side chain;

------- represents an optional bond;

R_2 and R_3 represent any possible amino acid side chain, or when the optional bond is present R_2 and R_3 represent together with the attached C and N atoms a proline ring which is optionally substituted with OH preferably in the 4-position or R_2 and R_3 represent a moiety of formula II or IIa;

R_1 represents an aromatic amino acid side chain;

p is 0 or 1;

n is 1, 2, 3 or 4;

and salts thereof.

91. A compound according to the preceding claims wherein R_8 represents H.

92. A compound according to any one of the two preceding claims wherein R_4 and R_5 are different or the same and represent the amino acid side chain of Gly or Ala.

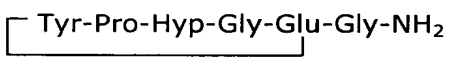
93. A compound according to any one of the three preceding claims wherein R_2 and R_3 represent together with the attached C and N atoms Pro or Hyp.

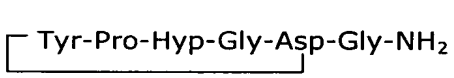
94. A compound according to any one of the four preceding claims wherein R_1 represents Tyr.

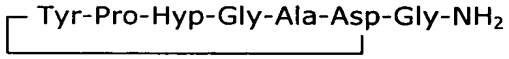
95. A compound according to any one of the five preceding claims wherein p is 1.

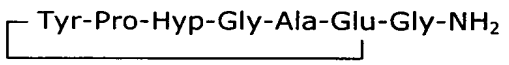
96. A compound according to any one of the six preceding claims wherein n is 1.

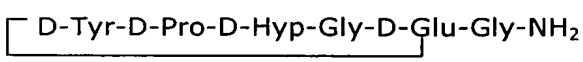
97. A compound of formula XV selected from the group consisting of

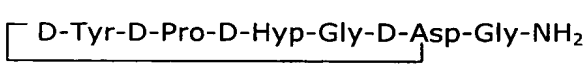


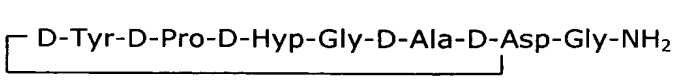


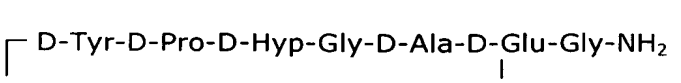












ad pharmaceutically acceptable salts thereof.

98. A peptide compound wherein the amino acid residues may be L- and/or D-forms, and having the general formula XVI

XVI R_1-Aa_1-Al-Aa_2-Ar-R_2

Wherein R_1 represents an optional amide bond between the N and the C terminal of the peptide, H or Ac;
Aa_1 represents a peptide sequence of between 0 and 4 amino acid residues;
Al represents an amino acid residue selected from the group consisting of Gly, beta Alanine and Sar;
Aa_2 represents an amino acid residue selected from the group consisting of Asn, Gln, Gly, Tyr, or a chemical unit, such as a hydroxy acid, an amino sulphonic acid, a phosphate group or a hydrocarbon chain connecting G and Ar via 4 covalent bonds;
Ar represents an aromatic amino acid residue, such as a Tyr, Trp, Phe, His, or Nal, optionally substituted with one or more substituents selected from the group consisting of halogen, such as F, Cl, Br, or I, OH, NO_2, NH_2, COOH, and CONH;
R_2 represents OH, NH_2 or is missing;
and retro analogues, retro all-D analogues (retro-inverse analogues) and salts thereof.

99. A compound according to the preceding claim wherein Aa_1 is selected from the group consisting of Ala, Gly-Ala, Gly-Asn-Tyr, and Gly-Asn-Tyr-Ala.

100. A compound according to any one of the two preceding claims wherein Al represents Gly or Sar.

101. A compound according to any one of the three preceding claims wherein Aa_2 represents Asn or Gln.

102. A compound according to any one of the four preceding claims wherein Ar represents Tyr or Phe optionally substituted with one or more halogen, such as I.

103. A compound according to any one of the five preceding claims wherein R_2 represents NH_2 when the compound is non-cyclic or R_2 is missing when the compound is cyclic.

104. A compound of formula XVI selected from the group consisting of
H-Gly-Ala-Gly-Asn-Tyr-NH_2,
cyclo(-Tyr-Ala-Ser-Ala-Gly-Asn-),
cyclo(-Tyr-Ala-Ser-Ala-Gly-Asn-),
cyclo(-Tyr-Gly-Asn-Tyr-Ala-Gly-Asn-),
cyclo(-Tyr-Val-Ser-Gly-Ala-Gly-Asn-),
Ac-Gly-Asn-Tyr-NH_2,
H-Gly-Asn-Tyr-NH_2,
Ac-Ala-Gly-Asn-Tyr-NH_2,
H-Ala-Gly-Asn-Tyr-NH_2, and pharmaceutically acceptable salts thereof.

105. A photo labile derivative of a compound of formula I, XII, XIII, XIIIa, XIV, XV or XVI herein, characterised in having covalently bound to the N-terminal N atom a photo probe selected from the group consisting of azido, diazo compounds including diazirines and thiadiazoles, optionally substitued nitrophenyl, and optionally substituted benzophenones.

106. A compound according to the preceding claim selected from the group consisting of Compound 31, 32, 33, 34 and salts thereof.

107. A thermo labile derivative of a compound of formula I , XII, XIII, XIIIa, XIV, XV or XVI herein, characterised in having covalently bound to the N-terminal N atom a thermo probe selected from the group consisting of maleimido, optionally substituted pyridyl disulphides, optionally substituted aliphatic halides, isothiocyantes and isocyanates, carbodiimides, activated esters, such as N-hydroxysuccinimide.

108. A compound according to the preceding claim which is $BrCH_2CO$-Gly-Asn-Tyr-NH_2 and salts thereof.

109. A compound according to any one of the preceding claims which shows antiarrhythmic effect in the Langendorf model described herein when used in a concentration of from of 10^{-13} to 10^{-7} M, or preferably in a concentration range of 10^{-12} to 10^{-9} M when diluted in medium.

110. A pharmaceutical composition comprising a compound of formulae I, XII, XIII, XIIIa, XIV, XV and XVI and formulae 2-12 or according to any one of the preceding claims, and a pharmaceutically acceptable carrier or diluent.

111. A composition according to the preceding claim which is an enteric tablet.

112. A composition according to claim 110 which is an injection preparation.

113. A method of increasing the gap junctional intercellular communication of mammalian cells subjected to glucose and/or oxygen deprivation comprising administering an effective amount of a compound of formulae I, XII, XIII, XIIIa, XIV, XV and XVI and formulae 2-12 or according to any one of claims 1-109 to said cells.

114. Use of a compound of formulae I, XII, XIII, XIIIa, XIV, XV and XVI and formulae 2-12 or according to any one of claims 1-109 for the preparation of a medicament.

115. Use of a compound of formulae I, XII, XIII, XIIIa, XIV, XV and XVI and formulae 2-12 or according to any one of claims 1-109 for the preparation of a medicament for the treatment of arrhythmia.

116. Use according to the preceding claim where said arrhythmia is a reentry arrhythmia of either atrial or ventricular origin, including repolarisation alternans arrhythmia where both supraventricular and ventricular tachyarrhythmias may present as tachycardia, flutter or fibrillation.

117. Use of a compound of formulae I, XII, XIII, XIIIa, XIV, XV and XVI and formulae 2-12 or according to any one of claims 1-109 for the preparation of a medicament for prevention and/or treatment of slowed conduction in the heart.

118. Use of a compound of formulae I, XII, XIII, XIIIa, XIV, XV and XVI and formulae 2-12 or according to any one of claims 1-109 for the preparation of a medicament for inproval of contractility of the heart.

119. Use of a compound of formulae I, XII, XIII, XIIIa, XIV, XV and XVI and formulae 2-12 or according to any one of claims 1-109 for the preparation of a medicament for treatment of diaease states associated with impaired GJIC during metabolic stress, including glucose and oxygen deprivation.

120. Use of a compound of formulae I, XII, XIII, XIIIa, XIV, XV and XVI and formulae 2-12 or according to any one of claims 1-109 for the preparation of a medicament for antithrombotic treatment.

121. Use of a compound of formulae I, XII, XIII, XIIIa, XIV, and XV and formulae 2-12 for the preparation of a medicament useful in prevention and /or treatment of osteoporosis.

122. Use of a compound of formulae I, XII, XIII, XIIIa, XIV, and XV and formulae 2-12 for the preparation of a medicament useful in prevention and /or treatment of joint diseases including arthritis.

123. Use of a compound of formulae I, XII, XIII, XIIIa, XIV, and XV and formulae 2-12 for the preparation of a medicament useful in prevention and /or treatment disease in poorly vascularized cartilage and joints including arthritis.

124. Use of a compound of formulae I, XII, XIII, XIIIa, XIV, and XV and formulae 2-12 for the preparation of a medicament useful in prevention and /or treatment of joint diseases including arthritis

125. Use of a compound of formulae I, XII, XIII, XIIIa, XIV, and XV and formulae 2-12 for the preparation of a medicament useful in prevention and /or treatment preventing bone loss and increase the healing of bone fractures.

126. Use of a compound of formulae I, XII, XIII, XIIIa, XIV, and XV and formulae 2-12 for the preparation of a medicament useful in prevention and /or treatment vascularization of the cornea in disease states with poor nutrition of the cornea and increase the healing of corneal lesions

127. Use of a compound of formulae I, XII, XIII, XIIIa, XIV, and XV and formulae 2-12 herein for the preparation of a medicament useful in treatment of wounds and in particular ischemic ulcers.

128. Use of a compound of formulae I, XII, XIII, XIIIa, XIV, and XV and formulae 2-12 herein for the preparation of a medicament useful in the treatment of gastric and duodenal ulcers.

129. Use of a compound of formulae I, XII, XIII, XIIIa, XIV, and XV and formulae 2-12 that increase gap junctional coupling and/or GJIC in the vascular wall for the preparation of a medicament for the prevention and/or treatment of hypertension.

130. Use of a compound of formulae I, XII, XIII, XIIIa, XIV, and XV and formulae 2-12 herein for the preparation of medicaments useful in preventing ischemic damage in the brain and for the treatment of organic psychoses that may present with symptoms, such as depression, anxiety, learning and memory deficit, fobias, or hallucinations.

131. Use of a compound of formulae I, XII, XIII, XIIIa, XIV, and XV and formulae 2-12 herein for the preparation of a medicament useful in prevention and /or treatment of cataract.

132. Use of a compound of formulae I, XII, XIII, XIIIa, XIV, and XV and formulae 2-12 herein for the preparation of a medicament useful in prevention and /or treatment of deafness associated with impaired GJIC.

133. Use of a compound formulae I, XII, XIII, XIIIa, XIV, and XV and formulae 2-12 for the preparation of a medicament useful in prevention and /or treatment of gastrointestinal motility disorders.

134. Use of a compound of formulae I, XII, XIII, XIIIa, XIV, and XV and formulae 2-12 for the preparation of a medicament useful in the treatment of female infertility that is due to poor cell-to-cell coupling in the ovaries.

135. Use of a compound of formulae I, XII, XIII, XIIIa, XIV, and XV and formulae 2-12 for the preparation of a medicament useful along with oxytocin for the induction and facilitation of labour.

136. Use of a compound of formulae I, XII, XIII, XIIIa, XIV, and XV and formulae 2-12 herein for the preparation of a medicament useful in treatment of male infertility associated with impaired cell-to-cell coupling.

137. Use of a compound of formulae I, XII, XIII, XIIIa, XIV, and XV and formulae 2-12 herein for the preparation of a medicament useful in improving glucose tolerance in a subject with non-insulin dependent diabetes mellitus due to impaired GJIC between β-cells.

138. A method of treatment of arrhythmia comprising administering to a patient in need of such treatment a therapeutically effective amount of a compound of formulae I, XII, XIII,

XIIIa, XIV, XV and XVI and formulae 2-12 or according to any one of claims 1-109.

139. A method of treatment according to the preceding claim wherein said arrhythmia is a reentry arrhythmia of either atrial or ventricular origin, including repolarisation alternans arrhythmia where both supraventricular and ventricular tachyarrhythmias may present as tachycardia, flutter or fibrillation comprising administering to a patient in need of such treatment a therapeutically effective amount of a compound of formulae I, XII, XIII, XIIIa, XIV, XV and XVI, formulae 2-12 or according to any one of claims 1-109.

140. A method of antithrombotic treatment comprising administering to a patient in need of such treatment a therapeutically effective amount of a compound of formula I, XII, XIII, XIIIa, XIV, XV or XVI or according to any one of claims 1-109.

141. A method of treatment of osteoporosis comprising administering to a patient in need of such treatment a therapeutically effective amount of a compound of formulae I, XII, XIII, XIIIa, XIV, XV and XVI, formulae 2-12 or according to any one of claims 1-109.

142. A method of treating or preventing bone loss and increase the healing of bone fractures comprising administering to a patient in need of such treatment a therapeutically effective amount of a compound of formula I, XII, XIII, XIIIa, XIV, XV or XVI or according to any one of claims 1-109.

143. A method of treatment of joint diseases including arthritis comprising administering to a patient in need of such treatment a therapeutically effective amount of a compound of formulae I, XII, XIII, XIIIa, XIV, XV and XVI, formulae 2-12 or according to any one of claims 1-109.

144. A method of treatment of cancer in tissue of endodermal, mesodermal or ectodermal origin, including carcinomas and hepatocellular and cholangiocellular neoplams and bone cancer comprising administering to a patient in need of such treatment a therapeutically effective amount of a compound of formulae I, XII, XIII, XIIIa, XIV, XV and XVI, formulae 2-12 or according to any one of claims 1-109.

145. A method of treatment wounds and in particular ischemic ulcers comprising administering to a patient in need of such treatment a therapeutically effective amount of a compound of formulae I, XII, XIII, XIIIa, XIV, XV and XVI, formulae 2-12 or according to any one of claims 1-109.

146. A method of treatment gastric and duodenal ulcers comprising administering to a patient in need of such treatment a therapeutically effective amount of a compound of formulae I, XII, XIII, XIIIa, XIV, XV and XVI, formulae 2-12 or according to any one of claims 1-109.

147. A method of treating or preventing hypertension by increasing gap junctional coupling and/or GJIC in the vascular wall comprising administering to a patient in need of such treatment a therapeutically effective amount of a compound of formula I, XII, XIII, XIIIa, XIIIa, XIV, XV or XVI or according to any one of claims 1-109.

148. A method of preventing ischemic damage in the brain and treating organic psychoses that may present with symptoms such as depression, anxiety, learning and memory deficit, fobias, or hallucinations comprising administering to a patient in need of such treatment a therapeutically effective amount of a compound of formulae I, XII, XIII, XIIIa, XIV, XV and XVI, formulae 2-12 or according to any one of claims 1-109.

149. A method of treating or preventing cataract comprising administering to a patient in need of such treatment a therapeutically effective amount of a compound of formulae I, XII, XIII, XIIIa, XIV, XV and XVI, formulae 2-12 or according to any one of claims 1-109.

150. A method of treatment of deafness associated with impaired GJIC comprising administering to a patient in need of such treatment a therapeutically effective amount of a compound of formulae I, XII, XIII, XIIIa, XIV, XV and XVI, formulae 2-12 or according to any one of claims 1-109.

151. A method of treatment of gastrointestinal motility disorders comprising administering to a patient in need of such treatment a therapeutically effective amount of a compound of formulae I, XII, XIII, XIIIa, XIV, XV and XVI, formulae 2-12 or according to any one of claims 1-109.

152. A method of treatment of female infertility that is due to poor cell-to-cell coupling in the ovaries comprising administering to a patient in need of such treatment a therapeutically effective amount of a compound of formulae I, XII, XIII, XIIIa, XIV, XV and XVI, formulae 2-12 or according to any one of claims 1-109.

153. A method of induction of and facilitation of labour comprising administering along with oxytocin to a patient in need of such treatment a therapeutically effective amount of a compound of formulae I, XII, XIII, XIIIa, XIV, XV and XVI, formulae 2-12 or according to any one of claims 1-109.

154. A method of treatment of male infertility associated with impaired cell-to-cell coupling comprising administering to a patient in need of such treatment a therapeutically effective amount of a compound of formulae I, XII, XIII, XIIIa, XIV, XV and XVI, formulae 2-12 or according to any one of claims 1-109.

155. A method of improving glucose tolerance in a subject with non-insulin dependent diabetes mellitus due to impaired GJIC between β-cells comprising administering to a patient in need of such treatment a therapeutically effective amount of a compound of formulae I, XII, XIII, XIIIa, XIV, XV and XVI, formulae 2-12 or according to any one of claims 1-109.

156. A method of treating or preventing disease in poorly vascularized cartilage and joints comprising administering to a patient in need of such treatment a therapeutically effective amount of a compound of formula I, XII, XIII, XIIIa, XIIIa, XIV, XV or XVI or according to any one of claims 1-109.

157. A method according to the preceding claim wherein said disease is arthritis.

158. A method of treating or preventing cataract comprising administering to a patient in need of such treatment a therapeutically effective amount of a compound of formula I, XII, XIII, XIIIa, XIIIa, XIV, XV or XVI or according to any one of claims 1-109.

159. A method of treating or preventing vascularization of the cornea in disease states with poor nutrition of the cornea and increase the healing of corneal lesions comprising administering to a patient in need of such treatment a therapeutically effective amount of a compound of formula I, XII, XIII, XIIIa, XIIIa, XIV, XV or XVI or according to any one of claims 1-109.

160. A method of treating or preventing growth and spreading of cancer cells comprising administering to a patient in need of such treatment a therapeutically effective amount of a compound of formula I, XII, XIII, XIIIa, XIIIa, XIV, XV or XVI or according to any one of claims 1-109.

161. A method of treatment of glucose and oxygen deprivation of cells, a tissue, or an organ in a patient suffering therefrom comprising administering to said patient an effective amount of a compound of formula I, XII, XIII, XIIIa, XIIIa, XIV, XV or XVI or according to any one of claims 1-109.

162. A method according to the preceding claim wherein said organ is the heart.